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EXAMINER	
CHAPPELL, CHERIE M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/605,266	AKELLA ET AL.	
	Examiner	Art Unit	
	Cherie M. Chappell	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,18-22,25,26,28,29 and 33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,18-22,25,26,28,29 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/04/2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Formal Matters

1. Applicant's Amendment and Response, dated 8 August 2005, is acknowledged and has been entered into the record. Claims 1-8, 18-23, 26, 28-29, and 33-40 are pending. Applicant's election of the species of platelet-derived growth factor (PDGF) on 9 January 2002 is acknowledged. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. In response to Applicant's Amendment and Response, dated 8 August 2005, the indicated allowability of claims 1-8, 28-29, 33-40 is withdrawn in view of new matter and newly discovered references to the depletion of histones from bone proteins, necessitated by Applicant's amendment. Rejections based on the newly cited references follow.

3. The indicated allowability of claims 18-23 is withdrawn in view of the newly discovered references to applying to a skin wound a composition of bone proteins. Rejections based on the newly cited references follow.

4. The indicated allowability of claim 26 is withdrawn in view of the newly discovered references to applying a composition of bone proteins to a wound area. Rejections based on the newly cited references follow.

Claim Rejections - 35 USC § 112, First Paragraph - Necessitated by Amendment

Enablement

5. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim recites at least one growth factor "derived" from bovine bone. However, neither the claim nor the specification teach how to "derive" at least one growth factor from bovine bone.

The invention is a method of using a heterologous mixture of bovine bone proteins. It is well known in the art that bovine bone protein mixtures contain hundreds of proteins, many of which have yet to be identified. It is also known that potentially beneficial growth factors are contained in these bovine bone mixtures. The relative skill of those in the art must necessarily be advanced in order to understand this complex mixture of proteins and their biochemical form and function. Alterations of the proteins contained in the bone protein mixture could result in a loss of function/activity due to structural changes in the proteins. The claim and the specification do not provide a standard for ascertaining the requisite degree of derivation such that one of ordinary skill in the art would be reasonably apprised of the invention. To what degree would the proteins be expected to be altered by a heat or chemical process? Thus, the level of predictability in extracting the potentially useful proteins from bovine bone is unpredictable. Applicants have not described what to do in the method in order to retain the functionality of the proteins for use in promoting skin wound or wound area healing. If the proteins which contain the healing properties are denatured or otherwise non-functional due to the process of deriving them from a bovine bone protein mixture, the method of using them would not be enabled.

In summary, the breadth with regard to the derivation of proteins from bovine bone is excessive. There is no guidance in the specification regarding how to derive proteins from bovine bone. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention. The guidance provided by the specification is not commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 112, First Paragraph - Necessitated by Amendment

Scope of Enablement

6. Claims 1-8, 18-23, 26, 28-29, and 33-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for skin wound healing in mice (specification p. 10, Table 1), does not reasonably provide enablement for other species, including humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It necessarily follows that in order to use a method to promote the healing of a skin wound, a subject with a wound in need of being treated must be present.

In the instant case, the only examples of subjects to be treated provided in the specification are nude mice, (see specification pages. 9-14, examples 1-3) and male Sprague-Dawley rats (specification page 15, example 4). Other than the two rodent examples provided, no other information is provided in the specification to indicate the genus of subjects to be treated with the claimed method of promoting

wound healing. No genus or species of subject to be treated are claimed. The skilled artisan could not begin to envision which subjects and/or other mammals to treat with the claimed method.

In summary, the breadth with regard to the subjects of treatment is excessive. There is no guidance in the specification regarding the subjects on which to carry out the steps of the claimed method because the promoting of healing of a skin would is not taught on any species other than nude mice and Sprague-Dawley rats. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention on any other species. The guidance provided by the specification is not commensurate with the full scope of the claims.

Claim Rejections - 35 USC § 112, First Paragraph - Necessitated by Amendment

Written Description

7. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claim recites at least one growth factor "derived" from bovine bone. However, neither the claim nor the specification describe how to derive at least one growth factor from bovine bone. The term "derived" is broad and indefinite. The American Heritage® Dictionary of the English Language (Fourth Edition 2000 by Houghton Mifflin Company) defines the term "derived" as "to produce or obtain from another substance by chemical reaction." Given the broadest reasonable interpretation, the claim and the specification do not provide a standard for ascertaining the requisite degree of derivation such that one of ordinary skill in the art would be reasonably apprised of the invention. How would the proteins be expected to be altered by the chemical process? Applicants have not described what changes need to be made in order to retain the functionality of the proteins. The claims and specification fail to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112, Second Paragraph - Necessitated by Amendment

8. Claims 1-5, 6-8,18-23, 26, 28-29, 33-40 are rejected under 35 U.S.C. 112, second paragraph as being incomplete fore omitting essential method steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to apply the bone protein mixture to a skin

wound or wound area. The skilled artisan would have to engage in excessive experimentation to determine how to apply the bone protein mixture.

9. Claims 1-8, 28-29, and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the method of depleting histones and/or ribosomes. The claims recite "depleted" (claim 1), "free" (claim 5), "substantially free" (claim 7), and "removed" (claim 37). The claims fail to teach how to deplete or remove histones and/or ribosomes from the claimed bone protein mixture. Claim 28 and Figure 15A specifically list a series of peptide fragments that are components of histones and ribosomes. It is unclear if these fragments are a part of the bone protein mixture as it is to be used by the claimed method or whether the claimed method would use a composition of whole proteins without any fragments of histones and/or ribosomes. If all histones and/or ribosomes, including their fragments, are to be removed, then the method should include the steps on how to do this. A skilled artisan could immunoprecipitate whole or partial histones or ribosomes, assuming they had antibodies that bound to exposed epitopes of the histones or ribosomes to be removed. However, it would be much more difficult and require excessive experimentation for an artisan to figure out how many antibodies would be required to remove histone and/or ribosome fragments from the bone protein mixture. The Applicants fail to teach the method of how to make the claimed bone protein mixture "free" or "substantially free" of histones and/or ribosomes. Several techniques are known in the art to purify proteins. However, many of these methods may alter the native conformation of proteins or alter their post-translational modifications. For example, proteins may be denatured by SDS-PAGE chromatography. Skilled artisans would have to engage in excessive experimentation to determine which methods of purification can be used to deplete or remove histones and/or ribosomes and/or their fragments so that at least one growth factor retains its native post-translational modifications.

10. Claims 1-5, 7, 8, 28, 29, and 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "depleted" (claim 1), "free" (claim 5), "substantially free" (claim 7), and "removed" (claim 37) as interchangeable terms related to the purification of histones and/or ribosomes from the bone protein mixture.

Claim 1 recites that ribosomes and/or histones are to be "depleted". "Depletion" of histones and/or ribosomes is not described in the specification. The term "depleted" in claim 1 is a relative term

that renders the claim indefinite. The term "depleted" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree of depletion. As such, the skilled artisan would not be reasonably apprised of the scope of the invention.

The term "free" in claim 5 is a relative term that renders the claim indefinite. The term "free" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "substantially free" in claim 7 is a relative term that renders the claim indefinite. It is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree of freedom. The skilled artisan would not be reasonably apprised of the scope of the invention. The term "removed" in claim 37 indicates that all histones and/or ribosomes have been taken out of the bone protein mixture. The amount or degree of removal is not taught in the method steps or in the specification. A person of ordinary skill in the art would not know how much of the histones and/or ribosomes would need to be removed in order to practice Applicant's invention. Thus, the degree of purification of histones and/or ribosomes is not clear.

This indefiniteness is compounded by the data provided in Figure 15A and claim 28. Tryptic digestion of the bone protein mixture results in protein fragments, including small histone and ribosome peptide fragments. The specification fails to describe how or whether these histone and/or ribosome peptide fragments would be removed from the bone protein mixture in order to meet the limitations of the terms "depleted", "free", "substantially free" and "removed.

In summary, neither the claims nor the specification teach the degree of purification of histones and/or ribosomes and their fragments that is required in order to practice the invention. Terms such as "deplete," "remove," "free," and "substantially free" all have different meanings and may mean different degrees of purification to those of ordinary skill in the art. Because histones are well know in the art to be highly antigenic, it would be important to know the degree of purity required in order to practice Applicant's method. The claims and specification fail to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Because claim 1 is not adequately described, all claims that depend on claim 1 are not adequately described.

11. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is improperly dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 28 depends from claim 1. Claim 1 recites a method comprising applying a composition comprising "BP (bone protein mixture) depleted of histones and/or ribosomes..." Claim 28 recites the method of claim 1 wherein the bone protein mixture is obtained from bovine bone and comprises the following tryptic peptide fragments..." including: SEQ ID NO: 1 (a claimed fragment of histone H1c), SEQ ID NO: 2 (a claimed fragment of 40s ribosome S20), SEQ ID NO:3 (a claimed fragment of LORP), SEQ ID NO: 12 (a claimed fragment of 60s ribosomal protein L32), SEQ ID NO: 16 (a claimed fragment of 60s ribosomal protein L6), SEQ ID NO: 17 (a claimed fragment of 60s ribosomal protein L6), SEQ ID NO: 18 (a claimed fragment of 60s ribosomal protein L6), and SEQ ID NO: 22 (a claimed fragment of histone H1.x). Dependent claim 28 contains fragments of histone and ribosomal proteins that claim 1 recites as having been depleted. Thus, claim 28 improperly depends from claim 1.

12. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 recites multiple amino acid sequences with parentheses around selected individual amino acids, alluding to possible amino acid substitutions or differences in individual amino acids between species in the listed highly-conserved tryptic peptide fragments (see also Figure 15A, which lists the same tryptic peptide sequences for mice, rats, and humans). Claim 28 also recites multiple SEQ ID. NOs which are specific to bovine amino acid sequences. It is unclear from the claim which species and amino acid sequences are being claimed. The sequences contained in the SEQ ID NOs differ from the amino acid sequences listed in the claims because the sequences in the SEQ ID NOs specify a particular species and do not contain parentheses around amino acids.

Claim Rejections - 35 USC § 103

13. Claims 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S patent 6177406 (Wang *et al.*, 2001) in view of European application EP 0433225 A1 (Cerletti et al., 1991), and further in view of Stelincki *et al.* (Plastic and Reconstructive Surgery, 1998, vol. 101, pp. 12-19) (all previously cited in Office Action of 5 May 2003). Claims 18-23 recite a method for promoting healing of a skin wound. Wang *et al.*, teach that BMP-3 can be used to treat burns and incisions (column 4, lines 29-31). Thus, the patent teaches the use of BMP-3 to treat skin wounds. Purification from bovine bone is taught

in column 5, lines 60-67, column 6, and column 7, lines1-4. Wang *et al.*, do not teach the use of TGF-β1/2/3, BMP-2/4-7, or FGF-1 to treat skin wounds.

EP 0 433 225 A1 teaches the use of "TGF-β-like" protein to treat burns and incisional wounds on p. 5, lines 13-16. TGF-β-like proteins are defined on p. 4, lines 53 and 54, to include TGF-β2 as well as TGF-β1 and TGF-β3. EP 0433225 A1 does not teach the use of BMP-2 or BMP-3 to treat skin wounds.

Stelincki *et al.*, teach the use of BMP-2 to skin incisions in fetal lambs. Stelincki *et al.*, do not teach the additional use of BMP-3 and TGF-β2 to treat skin wounds.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Wang *et al.*, with EP 0433225 Al, and Stelincki *et al.*, to administer a mixture of BMP-3 from natural or recombinant sources, together with BMP-2 and TGF-β1/2/or 3 for the purpose, as claimed in claims 18-23, because the two documents teach that they can be used for the same purpose. *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes: "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art." It would be obvious to one of ordinary skill in the art to combine the teachings of Stelincki *et al.* with those of Wang *et al.*, and EP 0 433 225 A1 to combine three or more factors (including, but not limited to BMP-4, BMP-5, BMP-6, BMP-7, and FGF-1) to treat wound healing, particularly when the multiple factor are related growth factors that are inherently present in purified bovine bone protein mixtures, as taught by Wang *et al.* One of ordinary skill would be motivated to combine multiple BMPs, TGF-β-1/2/3, and FGF-1 for the reasons that all of the growth factors in the bone protein mixture are known to be useful for the same purpose, they are already present in bovine bone protein mixtures, and it is therefore *prima facie* obvious to combine them. The skilled artisan would have reasonably expected success because all of the claimed growth factors, which are known in the art to promote wound healing, are already present in bovine bone protein mixture.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Chappell whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMC

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PRIMARY EXAMINER